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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,047	12/21/2001	Brian K. Kaspar	66671-092	5129

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MCDERMOTT, WILL & EMERY
4370 LA JOLLA VILLAGE DRIVE, SUITE 700
SAN DIEGO, CA 92122

EXAMINER	
PRIEBE, SCOTT DAVID	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/032,047	KASPAR ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/14/05 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required. Claims 1 and 9 recite the limitations "at least two months" and "at least four months," respectively, with respect to expression of the heterologous gene. This terminology was present in original claims 8 and 9, respectively, in the context of original claim 1. The specification does not disclose these limitations. The specification uses the term months only on page 19 in ¶ 0037, i.e. "period of months," in reference to the duration of heterologous gene expression from an AAV vector. Applicant is cautioned to avoid the introduction of new matter into the specification in overcoming this objection.

Claim Rejections - 35 USC § 112

Claims 1, 2, 4-7 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the reply of 4/30/04, claims 8 and 9 had been amended to recite that expression in human neurons was for at least two months or four months, respectively. These claims depend from claim 1, which is directed broadly to a "viral vector" being used in the claimed method. The claims require that the viral vector is limited to those that undergo retrograde transport following uptake at the synaptic portion of a neuron. In the instant reply, claim 1 has been amended to include the limitations of claim 8, such that the generic viral vector must also be capable of permitting heterologous gene expression to last two or more months. Only claim 3 is limited to a specific viral vector, AAV.

In the reply of 4/30/04, Applicant indicated that support for the amendment limiting the claims to transfection of human neurons was found in ¶ 0018, which is assumed to be the unlabeled paragraph following ¶ 0017 on page 8 of the specification, and original claim 19, directed to treatment of humans. However, neither of these locations indicate that the duration of expression in human neurons from a generic viral vector would last two or four months. As indicated above, these limitations have no antecedent basis in the specification. The only discussion of expression lasting for months is at page 19, ¶ 0037, specifically with respect to AAV vectors. Consequently, this new juxtaposition of limitations introduces new matter.

The claims require that the viral vector undergo retrograde transport following uptake at the synaptic portion of a neuron. The specification lists three viral vectors known in the prior art that were known to undergo retrograde transport, i.e. HSV, adenovirus and pseudorabies virus vectors (¶ 0018, pages 3-4), and describes AAV vectors as also undergoing retrograde transport. Original claim 1 embraced all four of these. Now, the claims require that expression of the heterologous gene from the viral vector also last at least two months. While the specification teaches that AAV vectors meet this requirement, it does not identify any other type of viral vector that does so. Rather, the specification (¶ 0018, pages 3-4) indicates that toxicity of HSV, adenovirus and pseudorabies virus vectors limit the duration of gene expression from these vectors. One of skill in the art of *in vivo* transfection with viral vectors would conclude from these teachings in the specification that unlike AAV vectors, heterologous gene expression from these three prior art viral vectors would be unlikely to last months.

Consequently, there is no evidence of record that Applicant was in possession of the generic invention now being claimed with respect to the broadly recited viral vector. The specification clearly describes only embodiments of the claimed invention wherein the viral vector is an AAV vector, which provides evidence of possession of only embodiments of the claimed invention wherein the viral vector is AAV. Limiting the claims to AAV vectors (with cancellation of claim 3) would overcome this rejection.

Claim Rejections - 35 USC § 102

Claims 1-4 and 9 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Aebischer et al., US 6,800,281.

Claims 1 and 5-7 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Aebischer et al., US 6,800,281.

Aebischer discloses a method of transducing neurons in a human by contacting the synaptic portion of a neuron with a lentiviral vector pseudotyped with rabies G protein comprising a heterologous nucleic acid. The vector undergoes retrograde transport to the cellular portion of the neuron, and the heterologous gene is expressed for up to eight months. See entire reference, especially col. 11-13.

With respect to claims 5-7, the claim requires that 1.5×10^7, 1.5×10^8, or 1.5×10^9 infectious particles of the viral vector (to be contacted) be "provided." The claims do not require that this amount be administered. If interpreted as broad as reasonably possible, the claim limitation means that these amounts be available at the time the method is carried out. Aebischer teaches to make viral vector stocks of up to 10^{10} transducing units per ml (t.u./ml) (col. 12-13). In the working examples, viral vector stocks at $3\text{-}5 \times 10^8$ t.u./ml were used, and 5-10 μl were injected into brains of rhesus monkeys, i.e. $1.5\text{-}5 \times 10^6$ t.u. per monkey (col. 37-38). Adult rhesus monkeys weigh between 4 and 10 kg, depending on age, sex, and level of obesity, or about 5-10% the weight of a human. While the specification does not explicitly teach the total number of t.u. to deliver to a human, one would assume that a dose proportional to that used in the monkeys would be a starting point, i.e. a 10-20-fold higher dose, i.e. $1.5\text{-}5 \times 10^7$. If a hospital were to treat more than one human, multiple doses of the vector would have to be available, i.e. provided.

Limiting the claims to use of an AAV vector would overcome this rejection.

Claim Rejections - 35 USC § 103

Claims 1, 2, 4-7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Horellou et al., US 2002/0031493 A1, or Finiels et al., US 6,632,427 B1, each in view of Zou et al. (Mol. Ther. 20(2): 105-113, Aug. 2000).

Horellou et al. discloses a method of treating Parkinson's disease by intrastriatal injection of an adenoviral vector comprising a therapeutic gene encoding GDNF. In a rat model system (the same as described in the instant specification), 1.5×10^8 pfu were injected into each rat. Neurons of both the striatum and substantia nigra were transfected. In the latter, transfection occurred via retrograde transport. Expression of GDNF protected the striatal and nigral neurons from death. It is evident that for treating humans, a substantially higher dose of vector would be required. See entire document, especially Example 4. Since the GDNF protects the neurons from apoptosis, it meets the limitation as being the product of an anti-apoptotic gene, as broadly interpreted.

Finiels discloses a method for treating ALS by intramuscular injection of an adenoviral vector expressing NT-3. Motor neurons are transfected via retrograde transport form the muscle. In SOD* mice, a model system for severe ALS, $5\text{-}10 \times 10^9$ pfu were injected, and the treatment extended the life span of the mice. It is evident that for treating humans, a substantially higher dose of vector would be required.

Neither Horellou nor Finiels disclose that the heterologous gene is expressed for at least two months, or at least four months in the case of claim 9.

However, Zou discloses that using conventional replication defective adenoviral vectors, such as the E1-deleted vectors used by Horellou and Finiels, for transduction of cells in the

central nervous system generates a substantial immune response to the vector causing substantial tissue damage and short duration of transgene expression. Zou compared the use of an E1-deleted adenoviral vector (fgAd) to that of a gutless adenoviral vector (hdAd) carrying a reporter gene for transfection of cells in the brain. No expression of the reporter gene was seen at a little over two months with the fgAd, whereas expression of the reporter from hdAd after 2 months was still about 50% of the maximum seen earlier post-transfection. Also, treatment with the hdAd produced a greatly reduced immune response as compared to fgAd, and little or no detectable tissue damage. With See Abstract for overview, and pages 105 and 111, and Fig. 4.

Therefore, it would have been obvious to have replaced the replication defective adenovirus vector of either Horellou nor Finiels with a gutless adenoviral vector, in order to greatly reduce the immune response produced by earlier adenoviral vectors, and the consequent tissue damage and shorter duration of expression, as taught by Zou. The results of Zou with the hdAd showing substantial heterologous gene expression for over two months (50% of maximum) indicate that at least some expression would occur at four months as well.
Limiting the claims to use of an AAV vector would overcome this rejection.

Claims 1-4 and 9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson et al. (European Journal of Neuroscience 12 (Suppl. 11): 233, Abstract 110.13, June 2000) for the reasons of record set forth in the Office action of 10/30/03.

Applicant's arguments filed 1/14/05 have been fully considered but they are not persuasive. Applicant simply rephrases the arguments presented in the reply of 4/30/04, which remain unpersuasive for the reasons of record set forth in the Office action of 7/14/04. It is noted

that claims 1-7 and 9 do not require any particular consequence of carrying out the method, e.g. successfully treating a disease. All that is required is that the vector be retrograde transported and the heterologous gene be expressed for a certain length of time. It is noted that the instant specification, like Peterson, does not demonstrate retrograde transport of AAV in human neurons or expression for at least two or four months in human neurons; the claimed invention is prophetic. In this regard, the instant specification adds no more to this art than was already suggested by Peterson, which used an animal model the same as described in the instant specification to support enablement of the instant prophetic invention for treating humans.

Double Patenting

Claims 1-7 and 9 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of copending Application No. 10/237,567 for the reasons of record set forth in the Office action of 10/30/03.

Applicant has deferred responding to the rejection until such time as allowable subject matter is indicated in one or both applications because the rejection is provisional.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER